Antidepressant Awareness

Part 4

Pharmacogenetics
Introduction

Pharmacogenetics is the science of how drugs are broken down and used – i.e. metabolised in the body.

Knowledge of pharmacogenetics is important for all doctors and people who take medications, because both slow i.e. poor and ultra fast metabolisers are genetically inefficient in metabolising drugs.
Extensive Metabolisers

Extensive Metabolisers (EMs) represent the norm for metabolising capacity.

Individuals with Extensive Metaboliser genotype can take medications at standard dose levels without incurring severe adverse reactions or toxic effects.
Poor Metabolisers

Slow/Poor metabolisers, have no metabolising activity whatsoever and it is unlikely that they will ever have a therapeutic response to any medication.

Side effects and adverse reactions will be more severe, because of increasing toxicity in the body i.e. poisoning.
Ultra, Intermediate and Poor Metabolisers

Ultra Metabolisers are inefficient metabolisers as medications either pass too quickly through the body having little or no effect or in the case of pro-drugs, toxic levels of the active metabolite build up rapidly.

Prodrugs are inactive until they are broken down in the body and converted to their active drug form. [http://en.wikipedia.org/wiki/Prodrug](http://en.wikipedia.org/wiki/Prodrug)

Drug companies have a wide range of medication doses and whilst Extensive Metabolisers are catered for to achieve the expected beneficial response at the higher dose range; Ultra Metabolisers taking prodrugs, Intermediate and Poor Metabolisers are not catered for, as for them, the lower dose range is the equivalent of taking an overdose.
Psychotropic/Psychiatric Drugs

75% of all psychotropic drugs are metabolised through CYP2D6 genetic enzyme pathway found mainly in the liver.

“Gene Testing Could Help Predict Drug Responses”
http://pnhw.psychiatryonline.org/content/40/10/33.1.full
Antidepressant Metabolisers

Most antidepressants are metabolised through CYP2D6 which is a highly variable enzyme. When people take antidepressants, variations of this enzyme i.e. Poor and Intermediate Metabolisers, will experience adverse drug reactions from antidepressant medications.
Antidepressants and Poor Metabolisers

10% of Caucasians, 40-50% of Asians, Pacific Islanders, African and African Americans are Poor Metabolisers (people with no functional metabolising activity - otherwise known as slow metabolisers) for CYP2D6.

10-20% of Africans and 3-6% of Caucasians are Poor Metabolisers for CYP2C19 which also metabolises some antidepressants.
Antidepressants and Intermediate Metabolisers

35% of Caucasians are Intermediate Metabolisers for CYP2D6 - this group are able to metabolise drugs but at about 50% rate; side effects build up slowly and appear later.

GENELEX: http://www.healthanddna.com/healthcare-professional/pharmacogenetics.html
Read the science:

“Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response.”

http://www.nature.com/mp/journal/v9/n5/full/4001494a.html
When patients are Poor, Intermediate, Ultra and/or any combination of these three metaboliser genotypes for antidepressants i.e. have gene variations, they will not experience the expected beneficial response.
Because of the genetic susceptibility to adverse reactions, these patients have more potential to develop serotonin syndrome, mania or psychosis.


Particular attention to the **CYP2D6** and the **CYP2C19** genetic status is needed to ascertain whether a patient will be able to tolerate antidepressants.

When people have **CYP2D6** and **CYP2C19** Poor and/or Intermediate Metaboliser genetic status, they would benefit by reducing the recommended antidepressant dose to avoid medication toxicities.
Read the science:

“CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards sub-population specific dosages.”

SSRI Antidepressants and Serotonin Transporter Gene

42% Caucasians have the short allele variant on the Serotonin Transporter Gene Promoter
http://www.nature.com/npp/journal/v23/n5/full/1395540a.html#bib7

The short allele variant is linked with emerging side effects:

Akathisia, agitation, insomnia, mania and delirium are all associated with the short allele
http://www.biologicalpsychiatryjournal.com/article/S0006-3223%2803%2900424-4/abstract

Delirium symptoms include hallucinations & delusions
Genes, Memes, Culture, and Mental Illness: Toward an ...
Natural variations in the **Serotonin Transporter Gene (SERT)** will result in a failure to achieve the expected beneficial response with SSRIs.

“**S allele of 5HTTLPR at the SLC6A4 locus is associated with a poor outcome after treatment with selective serotonin reuptake inhibitors**”


Deletion of long alleles in the serotonin transporter gene (5-HTT) is associated with a ‘powerfully predicted non response’

Other Variable Drug Metabolising Systems.

P-glycoproteins (P-gp’s)

U-glucuronisil transferases. (UGT’s)

Both P-gp and UGT variations affect the outcome of medications

The genotyping test for genetic variations could be vital for the individual to prevent misdiagnosis from antidepressant iatrogenic mania, psychosis and suicide.

It is important patients are informed about the genotyping test prior to taking antidepressants so that they have an awareness of their potential unsuitability which would incur negative effects.

Otherwise taking psychototropic/psychiatric drugs is not unlike taking street drugs with their unpredictable effects, e.g. hallucinations.
Newton’s third Law of motion states: “For every action there is an equal and opposite reaction”

With regard to Psychotropic/Psychiatric medication Jackson's First Law of Biopsychiatry states:

“For every action, there is an unequal and frequently unpredictable reaction.”

Jackson, Grace E. MD, Appendix D, Transcript of “What Doctors May Not Tell You About Psychiatric Drugs” Public Lecture, Centre for Community Mental Health - UCE Birmingham June 2004
A Genotyping Test is Worthwhile for Patient Safety

However, currently in mental health genotyping for psychotropics drugs is perceived as not financially worthwhile by UK regulatory bodies and the UK Government.

When the genotyping test is available for NHS general medicine patients, this practice is showing discrimination towards patients in mental health.
Genotyping Test

A genotyping test can be done with a simple mouth swab.

- AmpliChip CYP450 Test (Roche) for genotyping was launched in Europe in 2004. The test is now CE marked and available for diagnostic use in the European Union.

- AmpiChip was passed by the FDA for use in USA in January 2005, EU and Japan in 2004 and Korea in 2007.
Genotyping can be obtained privately from:

Genelex (USA)  www.genelex.com

This service is available for both professionals and the public. For patients a referral from a doctor is not necessary, as self referrals are accepted. The results are quick and sent to the recipient. A full follow up service is provided.
Potential Outcome when Genotyping Test not used

To quote from a pilot study of 100 inpatients:

“the findings suggested that CYP 2D6 deficiency may be associated with more medication side-effects and subsequently with non-compliance and rehospitalisations.”

“Pilot Study of the Cytochrome P-450 2D6 Genotype in a Psychiatric State Hospital.”
http://ajp.psychiatryonline.org/article.aspx?articleID=173007
Potential Outcome when Genotyping Test not used

“Fluoxetine (Prozac) - related death in a child with cytochrome P-450 2D6 genetic deficiency”.

The parents were investigated for murder and only after post mortem genotyping was carried out on the child, was the investigation dropped.

The test confirmed a variation in the **CYP2D6** gene, which metabolises Prozac antidepressant.
Genotyping Is Not the End of the Story

In addition to genotyping there could be many other factors that impede a person from efficiently metabolising drugs.

Genotyping could be used just as inappropriately as over-prescribing of psychotropic/psychiatric drugs. e.g. If the SERT and CYP profile results come back as efficient metabolisers then experts, if not adequately trained in pharmacogenetics, may mistakenly believe severe side effects have nothing to do with medications.

Consequently this assumption could be interpreted as a manifestation of an underlying ‘disease’ rather than the toxic effects of medication.
It needs to be remembered there are other variations and diversities in your genome, which may effect how you process antidepressant drugs.

Every person is different, One size does not fit all.
No one really knows how psychotropic drugs, or any other drugs, are processed in individuals.

The important thing is to be fully informed about likely side effects before taking any antidepressant drugs, and to think seriously about the alternatives and other options such as…

**Psychological Therapies**
Pharmacogenetic Education

It is important for doctors and pharmacists to be proficiently educated about pharmacogenetics in relation with antidepressant drugs.

This will enable mental health practitioners to be mindful that severe adverse reactions such as hallucinations, psychosis, suicidal ideation and mania may be antidepressant induced.

An awareness of pharmacogenetics for patients and professionals is empowering and contributes to safer drug use and a positive outcome.
Useful websites and papers:

**Super CYP Database:** A comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Preissner S., Kroll K., Dunkel M., Goldsobel G., Kuzmann D., Senger S., Günther S., Winnenburg R., Schroeder M. and Preissner R.  
[http://bioinformatics.charite.de/supercyp/](http://bioinformatics.charite.de/supercyp/)

**Psychotropic Medication and Cytochromes, Pharmacologicaliatrogenesis**  
Dr, Yolande Lucire  

Includes metaboliser type graph  
[http://www.prozactruth.com/drtphysician.htm](http://www.prozactruth.com/drtphysician.htm)

**Genelex Resources: Pharmacogenetics**  
Useful websites and papers:

Cytochrome P450 Enzymes and Psychopharmacology
Sheldon H. Preskorn, M.D. and Anne T. Harvey, Ph.D.
http://www.acnp.org/g4/GN401000086/CH085.html

Putting Pharmacogenetics into Practice
Michael M Hopkins et al
http://www.york.ac.uk/res/pgx/publications/nbt0406.pdf

New tool: Genotyping makes prescribing safer, more effective.
2D6 enzyme variations identify patients at risk for an unexpected response
David A. Mrazek, MD
The Journal of Family Practice Vol. 3, No. 9 / September 2004
http://www.jfponline.com/Pages.asp?AID=799
Contributors:

Catherine Clarke SRN, SCM, MSSCH, MBChA
Jan Evans MCSP. Grad Dip Phys

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